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MEMORANDUM

TO: Charles M. Andrews, Chief
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FROM: Anna M. Fan, Ph.D., Chief
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DATE: November 10, 2003

SUBJECT: METHYL BROMIDE: RESPONSE TO AUGUST 20, 2003 MEMORANDUM ON THE PROPOSED METHYL BROMIDE FIELD FUMIGATION REGULATIONS

The Office of Environmental Health Hazard Assessment (OEHHA) received your memorandum dated August 20, 2003 entitled "*Response to Oehha comments on the proposed methyl bromide field fumigation regulations*" and the accompanying memorandum from Lori Lim to Gary Patterson dated August 18, 2003 entitled "*Response to comments from the Office of Environmental Health Hazard Assessment of proposed methyl bromide field fumigation regulations*". This correspondence contained the Department of Pesticide Regulation's (DPR) responses to OEHHA comments and recommendations, contained in the OEHHA memoranda submitted to DPR dated June 13, 2003 and June 30, 2003 (OEHHA 2003a,b), regarding mitigation measures from seasonal exposures of agricultural workers to methyl bromide during soil fumigations and the proposed methyl bromide field fumigation regulations, respectively.

OEHHA prepared this present memorandum and the previous responses under various statutory authorities[1]. Also as indicated in your memorandum, the *Carillo* case settlement agreement requires DPR to consult with OEHHA pursuant to Food & Agr. Code section 14024.

Several areas of scientific disagreement continue to exist between OEHHA and DPR concerning the interpretation and application of the available toxicity data on methyl bromide and the proposed field fumigation regulations. In addition to these disagreements, there is an apparent misunderstanding by DPR of the events surrounding OEHHA's discussion with the Scientific Review Panel (SRP) regarding the derivation of the acute REL for methyl bromide, and the discussions that occurred at the SRP meetings in January and February 1999. This apparent misunderstanding has resulted in DPR raising concerns about how the 1 ppm 1-hour REL was "approved" by the SRP. The purpose of this memorandum is, therefore, two-fold: 1) to correct the record regarding the sequence of events that led to the development of OEHHA's acute REL of 1 ppm, and 2) to identify and explain the outstanding differences between the scientific data interpretation and approach used in providing public health protection regarding this issue.

SRP process of reviewing and approving Reference Exposure Levels

On page 5 of the August 18, 2003 memorandum from Lori Lim to Gary Patterson, DPR expressed "concern with how the 1 ppm 1-hour REL was 'approved' by the SRP" and presented selected quotes of the SRP transcripts to support this concern. We believe that DPR has made some incorrect assumptions about the process of SRP review of RELs and also has a misunderstanding of the discussion of the methyl bromide REL that occurred at the January and February 1999 SRP meetings. Dr. Lim was not listed as in attendance at the meetings she described in her memorandum. A literal reading of only the meeting transcript does not convey the visual and written communication that occurred at the meeting. A more accurate description of the sequence of events is as follows:

In January 1999 the SRP was in the process of reviewing OEHHA's document entitled "*Air Toxics Hot Spots Program Risk Assessment Guidelines Part I Determination of Acute Reference Exposure Levels for Airborne*" (OEHHA, 1999). This document described methodology for developing acute Reference Exposure Levels and the acute RELs for 51 chemicals and had undergone public comment and two workshops prior to the SRP meeting. The draft document,

[1] Health & Saf. Code section 59004 (OEHHA scientific consultation to programs in state agencies); Food & Agr. Code section 11454.1 (OEHHA's scientific peer review of risk assessments conducted by DPR); Food & Agr. Code section 12980 (joint and mutual responsibility with DPR for the development of regulations relating to pesticides and worker safety); Food & Agr. Code section 14022. ([a] DPR consultation with OEHHA over potential toxic air contaminants, [c] DPR shall consider all scientific data provided by OEHHA); and Food & Agr. Code section 14023 ([a] OEHHA participates with DPR in preparation of health effects reports on potential toxic air contaminants, [e] DPR consults with OEHHA regarding control measures for listed toxic air contaminants).

including the public comments and our responses, were provided to the Panel well in advance of the January 1999 SRP meeting. At that meeting, OEHHA addressed specific questions from the SRP on individual chemical RELs. OEHHA had proposed at the January meeting to adjust the acute REL for methyl bromide based on the Pharmaco LSR dog study from 1 ppm to 4 ppm by using time extrapolation to estimate a 1-hour hypothetical exposure from the 7-hour experimental exposure. This adjustment was proposed based on comments received during the public comment period.

On pages 5 and 6 of the August 18, 2003 memorandum, DPR stated that during the January 1999 SRP meeting, OEHHA provided erroneous information to the SRP about the 1942 Watrous study, which affected the acute REL.

The discussion that occurred at the January 1999 SRP meeting and the most pertinent points relating to the matter are summarized as follows:

1. At that meeting, Dr. Blanc expressed that he was not comfortable with OEHHA's new proposal for methyl bromide of 4 ppm as the acute REL. The transcript from the January 1999 meeting indicates that Dr. Blanc asked OEHHA about the Watrous (1942) study, which was correctly described in the document reviewed by the SRP. The SRP members read the written document prior to the meetings, which in fact was why Dr. Blanc asked about the human studies that were presented in the document as part of the toxicity summary for methyl bromide.

2. The response by OEHHA did indicate confusion on the part of Dr. Alexeeff regarding which study Dr. Blanc was asking about. This confusion was later acknowledged (see page 60 of the transcript).

3. Dr. Blanc asked OEHHA to return to the literature and review the human studies again to see if human data could be used in generating an acute REL (see page 54 of the transcript). OEHHA stated in several places that it would revisit the Watrous study and any case reports (page 55 of transcript).

4. OEHHA did revisit the human studies in the time between the January and February 1999 SRP meetings. An acute REL was derived by OEHHA from the Watrous (1942) study and this proposed revision was sent to the SRP for their review prior to the February 1999 meeting.

5. As noted above, the SRP members reviewed the written material as well as discussed the material at the meetings, which is the usual SRP process.

Thus, the temporary confusion on OEHHA's part during the discussion at the January 1999 SRP meeting regarding the Watrous study had no impact on the derivation of the acute REL from the Watrous study nor on the decision by the SRP to approve the acute REL. Both the initial draft document and the proposed revision contained a correct description of the Watrous (1942) study and thus, the SRP had read the appropriate description of the Watrous study as well as the derivation of the REL. DPR itself noted in footnote 7 of the August 18, 2003 DPR memorandum that the description of the Watrous study in the REL document was correct.

DPR stated that based on the transcript of the February meeting, the SRP still had erroneous information about the Watrous study (DPR August 18, 2003 memorandum page 7). This assumption is incorrect since the SRP had read the correct description of the Watrous study in both the initial written and revised methyl bromide REL summaries and, in addition, was presented with overheads of the REL derivation based on the Watrous study at the February 1999 meeting.

DPR further stated that additional incorrect information was provided to the SRP by OEHHA and was apparently concerned that the REL of 1 ppm was "approved" based on incorrect information. On page 7 of the August 18, 2003 memorandum, DPR stated that at the February 1999 SRP meeting, OEHHA claimed that a level of 4 ppm showed severe neurotoxicity in the dog study. OEHHA believes the transcript of the SRP meeting was misinterpreted by DPR. The following demonstrates that the SRP clearly understood that 4 ppm was the level OEHHA proposed to be protective against severe effects.

1. The documents reviewed by the SRP not only had derived acute RELs to use in risk assessment but also had derived levels protective against severe effects and levels protective against lethal effects for risk managers to understand the problems associated with exceedance of the REL. The OEHHA document, which the SRP reviewed, clearly showed derivation of a level, 4 ppm, protective against severe effects. That is to say, at 4 ppm no severe effects would be anticipated and the SRP knew that 4 ppm was the level protective against severe effects based on the dog study.

2. OEHHA had provided that information in written form twice and during the discussion (which included slides) at the January SRP meeting. At the bottom of page 7 of the August 18, 2003 memorandum, DPR referred to OEHHA's 1 ppm and 4 ppm RELs based on human and dog studies.

3. Since the SRP had reviewed and approved OEHHA's methodology for deriving acute RELs, it would not have accepted an REL of 1 ppm if severe effects occurred at 4 ppm. This would have run counter to OEHHA's approved standard methods which require at least a 300 fold uncertainty factor to extrapolate from a LOAEL in animals

to a NOAEL in humans (resulting in a hypothetical REL of about 0.01 ppm if 4 ppm was a level producing severe toxicity in the dog).

The SRP approved the document that described an REL of 1 ppm for mild effects and a level protective against severe effects of 4 ppm for methyl bromide. This demonstrates that the SRP clearly understood 4 ppm was the level protective against severe effects based on the dog study.

Remaining unresolved issues regarding interpretation of methyl bromide toxicity data and field fumigation regulations

Three continuing areas of disagreement persist between the two departments that, for the most part, arise from legitimate differences in scientific interpretation and application of the data: 1) Acute exposure target levels, 2) Subchronic exposure target levels, and 3) Health protectiveness of the target levels for infants and children. A fourth area, chloropicrin as an active ingredient, is in the process of being resolved. The following describes the remaining differences between the two departments.

1. Acute exposure target levels

DPR has calculated a target air concentration of 210 ppb to be used for buffer zone calculations, which was derived from a NOAEL of 40 ppm from a developmental toxicity study in rabbits. OEHHA proposed a target air concentration of 90 ppb calculated from a 1-hour Reference Exposure Level (REL) of 1 ppm that was based on symptoms observed in a worker exposure study. OEHHA expressed and documented its concerns regarding the assumptions and methods used in deriving this target air concentration as well as our conclusion that the value of 210 ppb may not be sufficiently protective of infants and children.

Additionally, as discussed in prior memoranda (OEHHA, 2003a), OEHHA agreed with the 210 ppb value, as it existed in *emergency regulations*. However, since the proposed regulations are now under consideration to become permanent, OEHHA believes it is appropriate to review the basis for regulatory standards.

Over the past 10 years, the two departments have both considered a number of approaches to evaluating acute risk from methyl bromide exposure. Our original proposed acute REL was 1 ppm based on the Breslin developmental study (OEHHA, 1995). Discussions following this proposal between DPR and OEHHA resulted in OEHHA selecting the Pharmaco LSR dog study as the basis of the acute REL. The calculation of the acute REL using the dog study and applying our standard methodology also resulted in a 1 ppm acute REL (OEHHA, 1998). Both OEHHA and DPR staff agreed upon a 1 ppm value for a one-hour exposure using severe neurological effects in the beagle study of Pharmaco-LSR, Inc. (1994) (OEHHA, 1997). In

December, 1998, as part of a response to public comment, OEHHA adjusted the REL utilizing Habers Law for time extrapolation and an empirically derived value for the exponent "n" in the equation $C^n \times T = K$. The adjusted REL was 4.45 ppm and was brought before the SRP for their review at the January 1999 meeting. This level is still in our final report as the level which protects against severe toxicity. The SRP at the January 1999 meeting indicated concern over the new approach based on their knowledge of the human literature and suggested that using the neurological effects in the dog study as the basis of the REL may not adequately protect the public. The SRP suggested that we go back to the human studies and try to utilize that data in development of an REL. This exercise resulted in the current REL of 1 ppm based on the Watrous (1942) study (OEHHA, 1999). OEHHA has consistently supported a 1-hour acute REL of 1 ppm for the past 10 years and has shown that it can be derived from three different studies.

We recognize the considerable uncertainties inherent in either extrapolation of the rabbit developmental study to humans or in the estimation of exposure to workers in the worker exposure study. Accordingly, the value to use as the target air concentration based on either study will be imprecise. Consequently, we believe that both the 1 ppm for 1-hour REL and 210 ppb for 24-hour REL should be considered. One may be more applicable than the other, depending on the actual exposure scenario. As indicated in the June 30, 2003 memorandum (OEHHA, 2003a), we look forward to a continuing discussion of the uncertainties surrounding the acute health effects from methyl bromide exposure and the identification of appropriate buffer zones following field fumigation.

2. Subchronic exposure target levels

OEHHA has calculated subchronic target levels of 1 and 2 ppb for residential and occupational exposures, respectively (OEHHA, 2003b). These values are based on our interpretation of the results presented in the Newton (1994) study in which we identified 5 ppm, the lowest dose tested, as a LOAEL. DPR proposes to adopt values of 9 and 16 ppb for residential and occupational exposures, respectively. DPR's values are based on the results of the Schaefer (2002) study, in which a NOAEL of 5 ppm was identified.

OEHHA's rational for selecting a LOAEL of 5 ppm either from the Newton (1994) or the Schaefer (2002) study has been documented previously (OEHHA, 2003a). We conclude that the results from the Schaefer (2002) study are not sufficiently compelling to identify 5 ppm as a NOAEL and to supercede the LOAEL identified in the Newton (1994) study. As indicated in DPRs toxicology data summary (DPR, 2003b), the results of the Schaefer study are unclear: "Because of the pivotal role of this study for determining the NOEL for subchronic exposure for risk assessment, it was reviewed by additional scientific staff (including the senior scientific staff) and by external peer-reviewers at the University of California, Davis. The consensus was that the 5 ppm exposure should be considered the NOEL, although this conclusion is judgmental and reasonable people may differ in the interpretation of the results." In light of the scientific

uncertainty regarding identifying the NOEL, we believe our interpretation is more protective of public health through treating the 5 ppm level as a LOAEL.

In addition to identifying 5 ppm as a LOAEL in DPR's toxicology summary, this value was also identified as a LOAEL in DPR's original RCD (DPR, 2002a) as well as in the September 2002 revision to the RCD (DPR, 2002b). We note that the September 2002 version of the RCD identified 5 ppm as a LOAEL even though the Schaefer (2002) study was on file at DPR. While DPR appears to have finalized its decision, OEHHA would look forward to further discussion with DPR staff of the appropriate NOAEL and uncertainty factor to apply in this situation.

3. *Health protectiveness of the target levels for infants and children*

OEHHA has expressed concerns regarding the data gap for developmental neurotoxicity of methyl bromide (OEHHA, 2003a,b). As indicated in DRP's RCD (DPR 2002a, p 127): "In this risk assessment for methyl bromide, inter-individual differences were accounted for by an uncertainty factor of 10. Given that methyl bromide is a potent neurotoxicant and there are inadequate toxicity information for infants and children, it may be prudent to consider an additional uncertainty factor to address the potential increased sensitivity for these population subgroups." Considering this data gap and the weakness of both the acute and subchronic data sets, OEHHA continues to have concerns that its own proposed acute and subchronic target values may not be sufficiently protective of infants and children. While OEHHA has not advocated a specific additional uncertainty factor to address this concern, we believe that this uncertainty is an important reason to err on the side of public health and consider 5 ppm to be a subchronic LOAEL for the dog studies. The basis for OEHHA's concerns are briefly summarized as follows:

- Children are considered to be more sensitive to some neuorotoxic effects than adults; the major toxic effects of methyl bromide are neurotoxicological in nature (for all durations of exposure).

- There is a data gap (under the Federal Insecticide and Rodenticide Act [FIFRA]) for a developmental neurotoxicity study.

- General weakness of the acute and subchronic data sets.

- The nature (neurotoxicity) and extent (permanent) of the toxicity of methyl bromide and the steep slope of the dose/response curve (points cited by the World Health Organization's advisory committee in supporting the use of an additional safety factor).

- A case report of an infant death (parents were intoxicated but recovered) from methyl bromide poisoning following fumigation of a nearby house.

Having stated these concerns, OEHHA does recognize the correction inherent in DPR's calculations using children's higher breathing rates versus those of adults as well as the use of a developmental endpoint for the derivation of the acute reference level, although it disagrees with the time-adjustment methodology, which is theoretically protective of sensitive subpopulations. Considering these health-protective choices, the adoption of 5 ppm as the subchronic LOAEL (Newton, 1994), the uncertainty factors (animal to human extrapolation, human variability and, for the case of the subchronic exposures, to convert a LOAEL to a NOAEL) applied to the calculation of the target values (both acute and chronic) tempers our concerns that potentially sensitive groups are not sufficiently protected. Accordingly, OEHHA would like to continue the discussion of the appropriateness of a safety factor for these sensitive subpopulations.

4. *Chloropicrin as an active ingredient*

DPR has responded favorably to OEHHA's suggestions regarding changes in the language to clarify that the proposed regulations pertaining to methyl bromide and health effects from methyl bromide exposure alone. Considering the recent chloropicrin incident that occurred in the town of Lamont in October 2003, OEHHA urges DPR to expedite the development of fumigation regulations for chloropicrin and chloropicrin/MeBr mixtures. OEHHA further recommends that DPR establish a task force comprised of interested parties to critically examine the issues of fumigation with chloropicrin as an active ingredient, either alone or in combination with methyl bromide. Otherwise, DPR's changes to the language of the final regulations (clarifying that the regulations pertain solely to methyl bromide) and their commitment to develop fumigation regulations specifically for chloropicrin are appropriate and responsive to OEHHA's suggestions.

Thank you for the opportunity to participate in the development of the proposed methyl bromide field fumigation regulations. If you have any additional questions or would like further clarification, please do not hesitate to call Dr. Anna Fan at (510) 622-3165, Dr. Melanie Marty at (510) 622-3154 or Mr. Robert Schlag at (916) 323-2624.

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